Gene Expression Modulated By Activation Of Microglia Or Macrophages

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Background of the Invention

Microglia have been implicated as key players in the inflammatory responses associated with numerous degenerative brain pathologies. For example, it has been shown that microglia activation is involved in such degenerative brain conditions as trauma, abscess, focal ischemia, experimental allergic encephalitis (EAE), Wallerian degeneration, Down's syndrome and Alzheimer's disease (Griffen et al., In: Biology and Pathology of Astrocyte-Neuron Interactions, pp. 359-381 (Fedoroff et al., eds., (1993); Carson et al., Soc. Neurosci., 24:634.8 (1998)). Recently, it has also been shown that during HIV infection, activation of the inflammatory response leads to astrogliosis and neuronal loss, pathologies that correlate with progressive AIDS dementia (Merrill et al., FASEB J., 5:2391-2397 (1991)).

Present information related to the characterization of microglial cells in their quiescent and various activated forms is incomplete. One hypothesis is that while the various microglial subtypes may arise from the differentiation of cells from a common precursor pool that is possibly indistinguishable from that giving rise to macrophage and dendritic cells, the roles played by differentiated microglia in normal neural physiology and neuropathology are determined in part by the ensembles of proteins that are expressed after their differentiation. Also, there may be overlapping ensembles expressed during different types of inflammation. In addition to the lack of information regarding quiescent and activated microglia phenotypes, due to the lack of phenotypic markers which distinguish microglial cells from macrophages, it has been difficult to discern the relative contribution of microglia versus infiltrating macrophages during the inflammatory response.

Recent studies indicate that within the central nervous system (CNS), microglia and macrophages are important reservoirs of HIV in infected patients (Gendelman et al., J. Leuk. Biol., 56:389-398 (1994); Perry et al., J. Leuk. Biol., 56:399-406 (1994); Dickson et al., Glia. 7:

75-83 (1993); McGeer et al., Glia, 7: 84-92 (1993); Spleiss et al., J. Neurosci. Res., 59:16-28 (1998)). HIV infection of microglia is thought to lead to their activation and result in the production of factors that initiate a cascade of neuropathological events, leading to a progressive dementia correlated with astrogliosis and neuronal loss (Wiley et al., Ann. Neurol., 29:651-657 (1991); Everall et al., J. Neuropathol. Exp. Neurol. 52:561-566; Lipton, Mol. Neurobiol. 8:181 (1994); Merrill et al., FASEB J., 5:2391-2397 (1991)).

The neurophysiology associated with HIV infection shares similarities with the neurodegenerative features observed in humans and experimental animal models of other neuropathological conditions, such as brain trauma, experimental allergic encephalitis (EAE), Wallerian degeneration after nerve transection, brain abscess, focal ischemia, Down's syndrome and Alzheimer's disease. See Griffin et al., In: Biology and Pathology of Astrocyte-Neuron Interactions, pp. 359-381 (Fedoroff et al., eds. (1993)); Stanley et al., J. Neuropathol. and Exp. Neurol., 53:231-238 (1994); Griffin et al., Neurosci. Lett., 176:133-136 (1994)). Further, many of the neuropathological findings have been observed in brains at autopsy of HIV-seropositive individuals in the absence of opportunistic infections, suggesting that these features are a direct consequence of HIV infection (Stanley et al., 1994).

The inflammatory processes that lead to neurodegeneration are presumably, at least in part, exaggerations of normal interactions between brain microglia, astroglia, oligodendrocytes and neurons. Such interactions may include, for example, those that normally facilitate synaptic plasticity in neurons, as well as those that facilitate myelinogenesis by oligodendrocytes. Evidence suggests that some of the molecules produced by activated microglia contribute to the neurodegeneration associated with HIV infection. For example, studies have shown that injection of interleukin-1 (IL-1), a product of activated microglia, can produce some of the neuropathologies associated with HIV-induced neurodegeneration (Giulian et al., J. Neurosci., 8:2485-2490 (1988)). Similarly, transgenic expression of the HIV envelope glycoprotein gp120 or transgenic expression of IL-6 by astrocytes, has been shown to mimic HIV-induced neuropathologies (Toggas et al., Nature, 367:188-193 (1994); Campbell et al., Proc. Natl. Acad. Sci., 90:10061-10065 (1993)).

In addition, nitric oxide (NO), produced by nitric oxide synthase (iNOS), an enzyme induced in activated microglia, has been shown to contribute to neuronal degeneration. For

example, it has been demonstrated in primary cortical cultures that nitric oxide mediates the neurotoxicity associated with human immunodeficiency virus type-1 coat protein (Dawson et al., Proc. Natl. Acad. Sci., 90:3256-3259 (1993); Wallas et al., Neuroreport, 5:245-248 (1993)). Others have reported both neuroprotective and neurodestructive effects of nitric oxide and related nitroso-compounds (Lipton et al., Nature, 364:626-632 (1993)). In addition, other studies have shown that the expression of two serine protease inhibitors is up-regulated in activated microglia and may play a role in brain inflammation (Thakker-Varia et al., Mol. Brain Res., 56:99-107 (1998)). One group has also reported a microglia gene product, human brain *mu* opioid receptor (MOR), that may play an anti-inflammatory role (Chao et al., J. Pharm. Exp. Therapeutics, 281:998-1004 (1997)). It is likely that additional products of microglial cells, presently unknown, contribute to the pathological process.

The microglia are bone marrow-derived cells of monocyte lineage that, like peripheral macrophages, demonstrate remarkable phenotypic plasticity dependent upon their environment. (Dawson et al., (1993); Wallas et al., (1993); Lipton et al., (1993)). While the exact relationship of microglia to macrophages has not been definitively determined, it is known that in addition to NO and IL-1, microglia produce an array of cytokines. In addition, several studies indicate that microglia may also serve as antigen-presenting cells during an inflammatory response (Frei et al., Eur. J. Immunol. 17:1271-1278 (1987); Carson et al., Glia 22:72-85 (1998)). Interestingly, Carson et al. has shown that mature microglia resemble immature antigen-presenting cells (Carson et al., 1998). Further studies demonstrate that CNS microglial cell activation and proliferation follow direct interaction with tissue-infiltrating T-cell blasts (Sedgewick et al., J. Immunol., 160:5320-5330 (1998)).

At least five forms of CNS macrophages have been described based on their morphologies and reactivity with reagents that recognize various macrophage cell surface antigens. These forms include amoeboid, ramified, activated, reactive, and perivascular microglia (Flaris et al., Glia 7:34-40 (1993)). Cumulatively, these forms account for 10-20% of the cells of the CNS, a percentage far greater than the concentration of macrophages found in peripheral tissues, which is fewer than 1% of the cells (Lawson et al., Neurosci., 39:151-170 (1990)).

are useful for identifying corresponding polypeptides in techniques such as western blotting, immunocytochemistry ,and ELISA assays using standard techniques such as those described in U.S. Patent No. 4,900,811.

Although the invention has been described with reference to the presently-preferred embodiments, it should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the claims.